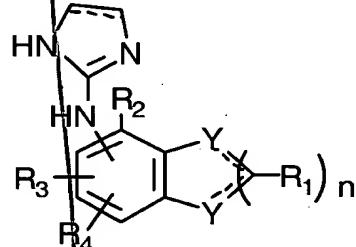


CLAIMS

Having now described the invention, what is claimed is:

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1) A topical ophthalmic composition useful for controlling elevated intraocular pressure associated with glaucoma and ocular hypertension while providing neuroprotection to the ocular nerves, comprising a combination of a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



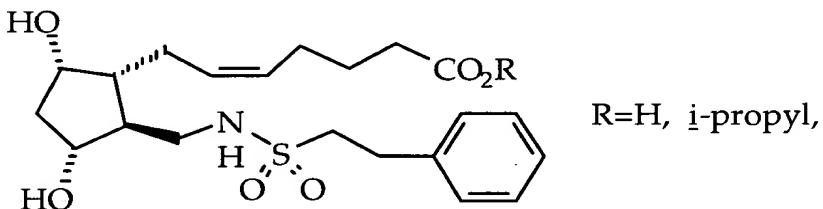
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH<sub>3</sub>, O, S and C-R<sub>1</sub>; R<sub>1</sub> is hydrogen, lower alkyl or oxo; R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or double bond, provided that two double bonds are not on the same carbon-in-the-case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

2) The composition of claim 1 wherein the prostaglandin is selected from the group consisting of PGF<sub>2α</sub>, PGE<sub>2</sub>, PGE<sub>1</sub>, prostacyclin, 15(S)-methyl-PGF<sub>2α</sub>, 16,16-dimethyl-PGF<sub>2α</sub>, 15(S)-methyl-PGE<sub>2</sub>, 16,16-dimethyl-PGE<sub>2</sub>, 17,18,19,20-tetranor-16-phenoxy-PGE<sub>2</sub>, 17,18,19,20-tetranor-16-phenoxy-PGF<sub>2α</sub>, 18,19,20-trinor-17-phenyl-PGE<sub>2</sub>, 18,19,20-trinor-17-phenyl-PGF<sub>2α</sub>, the free acid and lower alkyl esters of PGF<sub>2α</sub> wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, trimoprostil, RS-84-135, rioprostil,

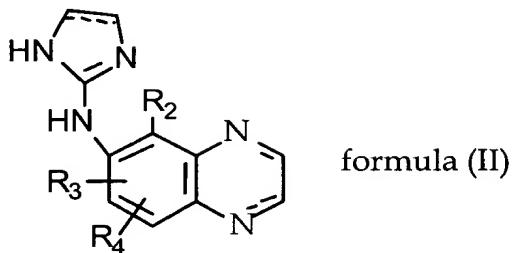
S-1033 (15-deshydroxy PGF<sub>2 $\alpha$</sub> , sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 5 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE<sub>2</sub>, 11-deoxy-PGF<sub>2 $\alpha$</sub> , 11-deoxy-16,16-dimethyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-PGF<sub>2 $\alpha$</sub> , misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, 10 alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

3) The composition of claim 2 wherein the prostaglandin is selected 15 from the group consisting of PGF<sub>2 $\alpha$</sub> -11-pivalyl ester, the 1-amido-15-methyl ether of PGF<sub>2 $\alpha$</sub> , 1-ethylamido-18,19,20-trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub> -1-ethyl ester, PGF<sub>2 $\alpha$</sub> -1-isopropyl ester, the acid and isopropyl ester derivatives of PGF<sub>2 $\alpha$</sub>  wherein the omega chain has been replaced 20 with phenylethylsulfonamidomethyl-, as represented by the structure below:



RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> -1-methyl ester.

25 4) The composition of claim 1 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R<sub>2</sub> is bromine or methyl and all other variables are defined as in claim 1.



5) The composition of claim 3 wherein the alpha adrenergic agent is  
brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-  
5 quinoxalinamine).

6) The composition of claim 4 wherein the alpha adrenergic agent is  
brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-  
10 quinoxalinamine).

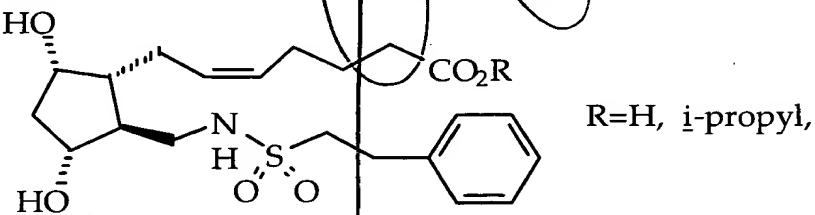
15 7) A method of treating a mammal suffering from glaucoma or ocular  
hypertension, comprising administering to the mammal a  
therapeutically effective amount of a prostaglandin and a  
therapeutically effective amount of an alpha adrenergic agent of  
formula (I)

Chemical structure of formula (I): A quinoxaline ring system. The 2-position is substituted with a 4,5-dihydro-1H-imidazol-2-yl group. The 6-position is substituted with an R<sub>2</sub> group. The 7-position is substituted with an R<sub>3</sub> group. The 8-position is substituted with an R<sub>4</sub> group. The structure is labeled "formula (I)" to the right. A dashed line with a bracket indicates a repeating unit, and the label "Y" is placed near the dashed line.

20 wherein each Y is independently selected from the group consisting of  
N, N-CH<sub>3</sub>, O, S and C-R<sub>1</sub>; R<sub>1</sub> is hydrogen, lower alkyl or oxo; R<sub>2</sub>, R<sub>3</sub>  
25 and R<sub>4</sub> are independently selected from the group consisting of  
hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer  
from 1 to 3; and a broken line beside a solid line indicates either a  
single or a double bond, provided that two double bonds are not on  
the same carbon in the case when n=1, and their pharmaceutically  
acceptable salts and esters as appropriate.

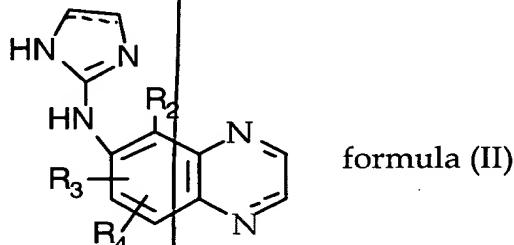
8) The method of claim 7 wherein the prostaglandin is selected from the group consisting of PGF<sub>2 $\alpha$</sub> , PGE<sub>2</sub>, PGE<sub>1</sub>, prostacyclin, 15(S)-methyl-PGF<sub>2 $\alpha$</sub> , 16,16-dimethyl-PGF<sub>2 $\alpha$</sub> , 15(S)-methyl-PGE<sub>2</sub>, 16,16-  
5 dimethyl-PGE<sub>2</sub>, 17,18,19,20-tetranor-16-phenoxy-PGE<sub>2</sub>, 17,18, 19,20-  
tetranor-16-phenoxy-PGF<sub>2 $\alpha$</sub> , 18,19,20-trinor-17-phenyl-PGE<sub>2</sub>, 18,19,20-  
trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> , the free acid and lower alkyl esters of  
10 PGF<sub>2 $\alpha$</sub>  wherein the omega chain has been replaced with  
phenylethylsulfonamidomethyl-, trimoprostil, RS-84-135, rioprostil,  
S-1033 (15-deshydroxy PGF<sub>2 $\alpha$</sub> , sodium salt), S-747260, nocloprost, CS-  
412, YPG-209, K-10134, cloprostenol, fluprostenol, luprostirol,  
etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519,  
ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK  
15 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-  
1206, UFO-21, 11-deoxy-PGE<sub>2</sub>, 11-deoxy-PGF<sub>2 $\alpha$</sub> , 11-deoxy-16,16-  
dimethyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-  
PGF<sub>2 $\alpha$</sub> , misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347,  
TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost,  
alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069,  
20 ONO-995 and RO-229648, and their pharmaceutically acceptable  
esters and salts, as appropriate.

9) The method of claim 8 wherein the prostaglandin is selected from the group consisting of PGF<sub>2 $\alpha$</sub> -11-pivalyl ester, the 1-amido-15-methyl  
25 ether of PGF<sub>2 $\alpha$</sub> , 1-ethylamide-18,19,20-trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub> -  
1-ethyl ester, PGF<sub>2 $\alpha$</sub> -1-isopropyl ester, the acid and isopropyl ester  
derivatives of PGF<sub>2 $\alpha$</sub>  wherein the omega chain has been replaced with  
phenylethylsulfonamidomethyl-, as represented by the structure below:



RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF<sub>2α</sub>-1-methyl ester.

5 10) The method of claim 7 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R<sub>2</sub> is bromine or methyl and all other variables are defined as in claim 7.



11) The method of claim 9 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

15 12) The method of claim 10 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

20 13) The method of claim 7 wherein the prostaglandin is the 11-pivalyl ester of PGF<sub>2α</sub> and the alpha adrenergic agent is brimonidine.

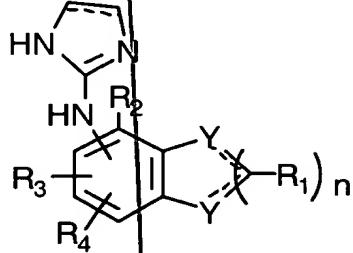
25 14) An article of manufacture comprising packaging material and a pharmaceutical combination of at least one alpha adrenergic agent and at least one prostaglandin and their pharmaceutically acceptable salts and esters as appropriate contained within said packaging material, wherein the pharmaceutical agents are effective in controlling elevated intraocular pressure associated with glaucoma and ocular hypertension and wherein the packaging material comprises a label which indicates that said combination can be used

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for control of elevated intraocular pressure or in treating glaucoma, and wherein said alpha adrenergic agent is represented by formula (I)



formula (I)

5 wherein each Y is independently selected from the group consisting of N, N-CH<sub>3</sub>, O, S and C-R<sub>1</sub>; R<sub>1</sub> is hydrogen, lower alkyl or oxo; R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or

10 double bond, provided that two double bonds are not on the same carbon in the case when n=1.

15 15) The article of claim 14 wherein the prostaglandin is selected from the group consisting of PGF<sub>2α</sub>, PGE<sub>2</sub>, PGE<sub>1</sub>, prostacyclin, 15(S)-methyl-PGF<sub>2α</sub>, 16,16-dimethyl-PGF<sub>2α</sub>, 15(S)-methyl-PGE<sub>2</sub>, 16,16-dimethyl-PGE<sub>2</sub>, 17,18,19,20-tetranor-16-phenoxy-PGE<sub>2</sub>, 17,18, 19,20-tetranor-16-phenoxy-PGF<sub>2α</sub>, 18,19,20-trinor-17-phenyl-PGE<sub>2</sub>, 18,19,20-trinor-17-phenyl-PGF<sub>2α</sub>, the free acid and lower alkyl esters of PGF<sub>2α</sub> wherein the omega chain has been replaced with

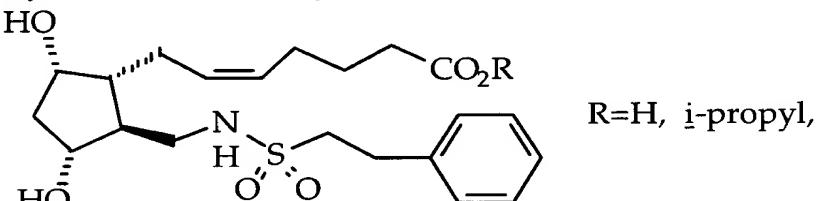
20 phenylethylsulfonamidomethyl-, trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF<sub>2α</sub>, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luprostirol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK

25 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE<sub>2</sub>, 11-deoxy-PGF<sub>2α</sub>, 11-deoxy-16,16-dimethyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-PGF<sub>2α</sub>, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069,

ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

16) The article of claim 15 wherein the prostaglandin is selected from the group consisting of PGF<sub>2 $\alpha$</sub> -11-pivalyl ester, the 1-amido-15-methyl ether of PGF<sub>2 $\alpha$</sub> , 1-ethylamido-18,19,20-trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub> -1-ethyl ester, PGF<sub>2 $\alpha$</sub> -1-isopropyl ester, the acid and isopropyl ester derivatives of PGF<sub>2 $\alpha$</sub>  wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:

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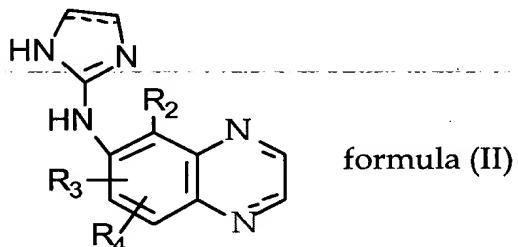


RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> -1-methyl ester.

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17) The article of claim 14 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R<sub>2</sub> is bromine or methyl and all other variables are defined as in claim 14.

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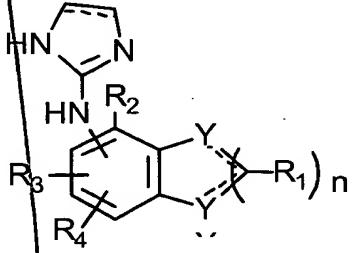
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18) The article of claim 16 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

19) The article of claim 17 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

5 20) The article of claim 14 wherein the prostaglandin is the 11-pivalyl ester of PGF<sub>2α</sub> and the alpha adrenergic agent is brimonidine.

10 21) A method of preventing degeneration of the optic nerve and providing protection of the retinal ganglion cells of a mammal suffering from glaucoma or ocular hypertension, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)

15 

formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH<sub>3</sub>, O, S and C-R<sub>1</sub>; R<sub>1</sub> is hydrogen, lower alkyl or oxo; R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken-line beside a solid-line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

20 22) The method of claim 21 wherein the prostaglandin is selected from the group consisting of PGF<sub>2α</sub>, PGE<sub>2</sub>, PGE<sub>1</sub>, prostacyclin, 15(S)-methyl-PGF<sub>2α</sub>, 16,16-dimethyl-PGF<sub>2α</sub>, 15(S)-methyl-PGE<sub>2</sub>, 16,16-dimethyl-PGE<sub>2</sub>, 17,18,19,20-tetranor-16-phenoxy-PGE<sub>2</sub>, 17,18,19,20-tetranor-16-phenoxy-PGF<sub>2α</sub>, 18,19,20-trinor-17-phenyl-PGE<sub>2</sub>, 18,19,20-trinor-17-phenyl-PGF<sub>2α</sub>, the free acid and lower alkyl esters of

PGF<sub>2 $\alpha$</sub>  wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF<sub>2 $\alpha$</sub> , sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luprostirol, 5 etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE<sub>2</sub>, 11-deoxy-PGF<sub>2 $\alpha$</sub> , 11-deoxy-16,16-dimethyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-PGE<sub>2</sub>, 11-deoxy-15(S)-methyl-10 PGF<sub>2 $\alpha$</sub> , misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostene, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

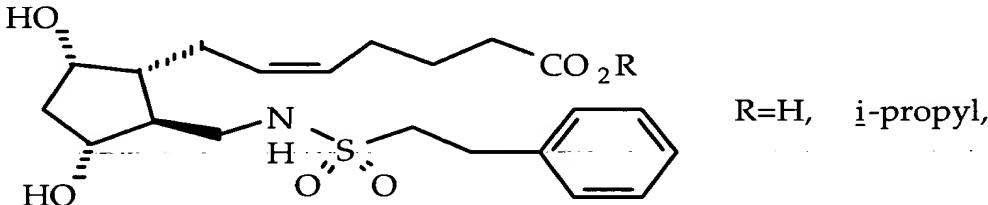
15 23) The method of claim 22 wherein the prostaglandin is selected from the group consisting of PGF<sub>2 $\alpha$</sub> -11-pivalyl ester, the 1-amido-15-methyl ether of PGF<sub>2 $\alpha$</sub> , 1-ethylamido-18,19,20-trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub> -1-ethyl ester, PGF<sub>2 $\alpha$</sub> -1-isopropyl ester, the acid and isopropyl ester derivatives of PGF<sub>2 $\alpha$</sub>  wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:

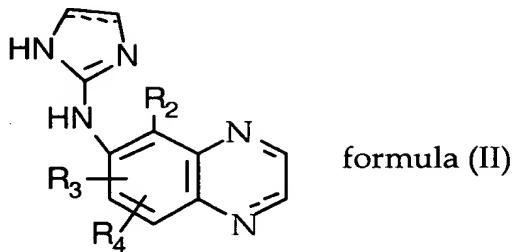
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RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF<sub>2 $\alpha$</sub> -1-methyl ester.

30 24) The method of claim 21 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R<sub>2</sub> is bromine or methyl and all other variables are defined as in claim 21.





25) The method of claim 23 wherein the alpha adrenergic agent is  
brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-  
5 quinoxalinamine).

26) The method of claim 24 wherein the alpha adrenergic agent is  
brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-  
quinoxalinamine).

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27) The method of claim 21 wherein the prostaglandin is the 11-  
pivalyl ester of PGF<sub>2 $\alpha$</sub>  and the alpha adrenergic agent is brimonidine.

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